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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,952	01/25/2001	Gregory Donoho	LEX-0118-USA	5907

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/769,952	DONOHO ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *15 March 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-3 and 5-7*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Notice of References Cited PTO-892*

ADVISORY ACTION

[1] Applicants' request for reconsideration, filed March 15, 2004, is acknowledged. However, applicants' response does not place the application in condition for allowance for the reasons stated below. It is noted that applicants' request for reconsideration does not include an amendment to the claims.

[2] The rejections of claims 1-3 and 5-7 under 35 USC §§ 101 and 112, first paragraph, are maintained for the reasons of record (as set forth in items [6] and [8] of the Office action mailed December 10, 2003) and for the reasons stated below. Applicants argue that because the polypeptide encoded by SEQ ID NO:1 has been annotated as a nitrilase polypeptide by an unaffiliated third party, there can be no question that one would believe SEQ ID NO:2 is a human nitrilase protein. Applicants argue that one would recognize the usefulness of the claimed nucleic acid as the protein encoded thereby allegedly interacts with a known tumor suppressor and allegedly has a role in cancer. Applicants' argument is not found persuasive.

Applicants' arguments appear to address the issue of credibility of an asserted utility. However, the credibility of asserted utility is not at issue – instead it is the examiner's position that the specification provides no specific and substantial asserted utility for the claimed invention because the asserted utilities either apply to the general class of polynucleotides or require further experimentation to identify a "real-world" use. It should be emphasized that the specification does not assign a function to the polypeptide of SEQ ID NO:2 and provides no disclosure that SEQ ID NO:1 has a role in cancer or that SEQ ID NO:2 interacts with a tumor suppressor as asserted by applicants. Instead, the specification merely indicates that SEQ ID NO:2 shares an undisclosed level of structural similarity to nitrilase proteins from other organisms (see page 2, top) – this not an assertion of function and the examiner has not interpreted this statement as such. Even assuming the specification asserts SEQ ID NO:2 has nitrilase activity – which it does not – it is noted that further experimentation is required to establish a "real world" use for the claimed invention as the biological significance of nitrilases remains to be determined as evidenced by Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9) as stated in a previous Office action. Furthermore, regarding the reference of Pace et al. (*Curr Biol* 10:907-917), who assign nitrilase enzymatic activity to a

polypeptide identical to SEQ ID NO:2 (referred to as "Nit2" by Pace et al.) and provide evidence that Nit2 interacts with a tumor suppressor, it is noted that this reference was NOT available to one of ordinary skill in the art at the time of the invention. MPEP 2164.05(a) makes clear that the specification must be enabling as of the filing date of the application and, while MPEP 2164.05(a) states, "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public," it is noted that the teachings of Pace et al. (*Curr Biol* 10:907-917) were not available to the public at the time of the invention. Even assuming arguendo the reference of Pace et al. (*Curr Biol* 10:907-917) were available to a skilled artisan at the time of the invention, there is no evidence of record that would indicate the biological significance of this interaction and how would exploit this interaction for a therapeutic or diagnostic use. Therefore, even if the specification disclosed or it was well-established at the time of the invention that SEQ ID NO:2 interacts with a known tumor suppressor, this disclosure alone – without further guidance – is insufficient to establish a "real-world" utility for the claimed invention.

Applicants argue that the examiner's statement regarding the specification's failure to assert function of the polypeptide of SEQ ID NO:2 is at odds with the examiner's suggested title for the instant specification, i.e., "Nucleic Acid Encoding a Human Nitrilase Polypeptide". Applicants argue that the examiner "clearly understands that the specification as originally filed does in fact 'assign a function to the polypeptide of SEQ ID NO:2'". Applicants argue that the examiner's argument that the specification does not assert a function for SEQ ID NO:2 is without merit and does not support the examiner's position that the claimed invention lacks patentable utility. Applicants' argument is not found persuasive.

It is noted that the title of the specification as originally filed was "NOVEL HUMAN ENZYMES AND POLYNUCLEOTIDES ENCODING THE SAME". MPEP 606.01 directs the examiner to "require the substitution of a new title that is clearly indicative of the invention to which the claims are directed" when the title is not descriptive of the invention claimed. MPEP 606.01 states, "[t]his may result in slightly longer titles, but the loss in brevity of title will be more than offset by the gain in its informative value in indexing, classifying, searching, etc." As the original title has little informative value, the examiner, in accordance with MPEP 606.01 suggested a title that is more descriptive using specific key words disclosed in the

specification. The prosecution record is quite clear with respect to the examiner's position that the specification fails to assert a function for the polypeptide of SEQ ID NO:2 (see page 2, bottom to page 3, top of the Office action mailed December 10, 2003) and the examiner's suggested title is in no way a substitute for the specification's failure to assert a function for the polypeptide of SEQ ID NO:2, which is the polypeptide encoded by the claimed polynucleotide. In this case, the specification fails to assert a function for the polypeptide encoded by SEQ ID NO:1 and a skilled artisan would not understand the disclosure the disclosure of "[t]he novel human proteins (NHPS) described for the first time herein share structural similarity with nitrilase proteins from a wide variety of living organisms" (page 2, lines 1-3 of the specification) as providing an assertion of the function of the polypeptide encoded by SEQ ID NO:1. Instead, while the specification suggests the polypeptide encoded by SEQ ID NO:1 has structural similarity to nitrilases, there is no indication that the polypeptide encoded by SEQ ID NO:1 exhibits nitrilase enzymatic activity. Even if the specification made such an assertion, the state of the art as evidenced by Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9) teaches that the term "nitrilase" encompasses members having diverse enzymatic activities (page 4, Table I) and that the biological significance of Nit nitrilases is unknown (page 7, right column, bottom). Thus, even if the specification asserted that SEQ ID NO:1 encodes a polypeptide having nitrilase activity – which it does not – it is unclear from the specification as to which of the numerous activities encompassed by the term "nitrilase" would be exhibited by the encoded polypeptide.

Applicants argue that the disclosure that the sequences are "nitrilase-like" is evidence of an asserted function for the polypeptide encoded by SEQ ID NO:1. Applicants argue that the examiner appears to require an example demonstrating that the claimed sequence has nitrilase activity, which applicants allege, is unsupported by legal precedent as there is no requirement for the disclosure of a specific example (citing *In re Gay*, 135 USPQ 311 (CCPA 1962)). Applicants' argument is not found persuasive.

It should be noted that nowhere in the specification is there a disclosure that SEQ ID NO:1 and 2 are "nitrilase-like" as asserted by applicants. The only reference to a sequence being "nitrilase-like" in the specification is the following: "SEQ ID NOS:15 describe representative a nitrilase-like ORF with flanking

sequences" (page 2, lines 30-32 of the specification). This statement refers only to SEQ ID NO:15 – not to SEQ ID NO:1 and 2. As stated above, the specification fails to assert a function for the polypeptide encoded by SEQ ID NO:1 and a skilled artisan would not understand the disclosure of "[t]he novel human proteins (NHPS) described for the first time herein share structural similarity with nitrilase proteins from a wide variety of living organisms" (page 2, lines 1-3 of the specification) to provide such an assertion. An assertion of structural similarity is not an assertion of functional similarity as highly structurally similar proteins may have different functions (see, e.g., Seffernick et al. J Bacteriol 183:2405-2410; cited in the Office action mailed May 16, 2003) and similar functions may be found in structurally unrelated proteins (see e.g., Hegyi et al. J Mol Biol 288:147-164, particularly page 148, right column). Thus, while structural similarity may suggest the possibility of functional similarity, it does not assure it and cannot be taken as an assertion that this is the case. Applicant did not make this assertion in the specification i.e., the assertion that the polypeptide encoded by SEQ ID NO:1 has nitrilases enzymatic activity. The examiner's invitation for applicants to direct his attention was made in the event that the examiner has inadvertently overlooked an assertion of function of the polypeptide encoded by SEQ ID NO:1. However, the disclosure that the polypeptide encoded by SEQ ID NO:1 shares structural similarity with nitrilases has been interpreted ONLY as relating to the structure of SEQ ID NO:1, not to its function.

Applicants argue the present situation appears to track Example 10 of the Revised Interim Utility Guidelines Training Materials (hereafter referred to as the "Utility Guidelines"). Applicants argue that Example 10 of the Utility Guidelines allegedly establishes that a utility rejection is not proper when a full length sequence has a similarity score >95% to a protein having a known function. Applicants argue that the Utility Guidelines indicate that the claims meet the utility requirement. Applicants' argument is not found persuasive.

Contrary to applicants' assertion, the present situation does not track Example 10 of the Utility Guidelines, at least for the following reasons. Example 10 states that the specification asserts that the polynucleotide encodes a DNA ligase and has a similarity of >95% to known DNA ligases and provides an alignment with known DNA ligases, however the instant specification fails to assert that SEQ ID NO:1 encodes a nitrilase, fails to identify the level of homology or similarity between SEQ ID NO:2 and other

known nitrilases, and fails to provide any alignment that would suggest homology or similarity. Furthermore, it is noted that the nucleic acid of Example 10 encodes a polypeptide that is well characterized and has a specific enzymatic activity, i.e., DNA ligase activity. In contrast to Example 10, the term "nitrilase" is non-specific as the nitrilase superfamily encompasses members having diverse enzymatic activities as evidenced by Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9) who also teach that the substrate and cell biology of nitrilases remain to be determined. A second difference is that Example 10 states that a search of the "prior art" confirms the high level of homology between the encoded polypeptide and other DNA ligases. While it is noted that Pace et al. (*Curr Biol* 10:907-917) assign nitrilase enzymatic activity to a polypeptide identical to SEQ ID NO:2 (referred to as "Nit2" by Pace et al.), it is noted that this reference was NOT available to one of ordinary skill in the art at the time of the invention. MPEP 2164.05(a) makes clear that the specification must be enabling as of the filing date of the application and, while MPEP 2164.05(a) states, "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public," it is noted that the teachings of Pace et al. (*Curr Biol* 10:907-917) were not available to the public at the time of the invention. Therefore, such information would not have been available to a skilled artisan at the time of the invention. A third difference is that the DNA ligase of Example 10 has a "well-established" utility, while the polypeptide encoded by SEQ ID NO:1 of the instant application has no "well-established" utility as evidenced by Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9). Contrary to Example 10, further experimentation is clearly required to determine a "real-world" use for the instant invention.

Applicants argue that the publication date of Pace et al. (*Curr Biol* 10:907-917), which is after the filing date of the instant application, is irrelevant with regard to the issue of utility. Applicants argue the Pace et al. (*Curr Biol* 10:907-917) reference is evidence that other skilled artisans have confirmed the involvement of the claimed polynucleotide in cancer, as asserted by the specification and that the examiner's argument does not support a lack of utility. Applicants' argument is not found persuasive.

It should be noted that the specification fails to assert that the polynucleotide of SEQ ID NO:1 or the polypeptide encoded thereby is involved in cancer. Instead, the specification asserts that "[e]nzyme

abnormalities have thus been associated with, inter alia, growth, development, protein and cellular senescence, cancer, or other diseases" (page 1, lines 27-29) and there is no disclosed abnormality in the polypeptide encoded by SEQ ID NO:1 correlated with any of the disclosed disorders, including cancer. Furthermore, it should be noted that an assertion that a particular polynucleotide is involved in or has a role in cancer *is not an assertion of utility* as it is unclear as to how a skilled artisan is to use the polynucleotide based on such an assertion. Even if such a use for SEQ ID NO:1 or the polypeptide encoded thereby were asserted, e.g., use for treating or detecting cancer, the specification fails to provide the guidance necessary for treating cancer or detecting cancer. As acknowledged by applicants, the teachings of Pace et al. (*Curr Biol* 10:907-917) were not available to a skilled artisan at the time of the invention and contrary to applicants' assertion, the publication date of Pace et al. (*Curr Biol* 10:907-917) is highly relevant to the instant rejection. MPEP 2164.05(a) makes clear that the specification must be enabling as of the filing date of the application and while MPEP 2164.05(a) states, "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public," it is noted that the teachings of Pace et al. (*Curr Biol* 10:907-917) were not available to the public at the time of the invention. Other than the reference of Pace et al. (*Curr Biol* 10:907-917), which was not available at the time of the invention, there is no indication in the specification that the polypeptide of SEQ ID NO:2 was associated with any tumor suppressor. Moreover, even assuming arguendo Pace et al. (*Curr Biol* 10:907-917) was available at the time of the invention – which it was not – contrary to applicants' assertion, this reference does not confirm the involvement of the claimed polynucleotide in cancer. While it is acknowledged that Pace et al. (*Curr Biol* 10:907-917) make the discovery that human Nit interacts with Fhit, a tumor suppressor, Pace et al. teach that further experimentation is required to elucidate the role of Nit in maintaining a differentiated cellular state. Furthermore, Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9) teach that the relationship of Nit to tumor suppression is "not known" (page 7, right column, bottom). Thus, even assuming arguendo Pace et al. were available to a skilled artisan at the time of the invention, further experimentation is required as evidenced by Pace et al. (*Curr Biol* 10:907-917) and Pace et al. (*Genome Biol*

2:reviews0001.1-0001.9) to determine the role of Nit proteins in maintaining cellular differentiation and tumor suppression, which clearly supports the examiner's position.

Applicants argue that the standard for satisfying the requirements of 35 USC 101 is not whether further or additional experimentation is required, but whether undue experimentation is required to practice the claimed invention. Applicants argue that the "widespread knowledge" of the interaction between Fhit and members of the nitrilase family in invertebrates along with extensive similarities between Fhit and the nitrilase family between invertebrates and mammals strongly argues against a use requiring undue experimentation. Applicants argue that the need for some additional experimentation does not render the claimed invention unpatentable and a considerable amount of experimentation may be permissible if it is routinely practiced in the art and that a patent need not disclose what is well known in the art. Applicants' argument is not found persuasive.

It is noted that the only evidence of Fhit-Nit2 (Nit2 has 100% identity with the polypeptide encoded by SEQ ID NO:1) interaction is provided by the reference of Pace et al. (*Curr Biol* 10:907-917), which was unavailable at the time of the invention. Other than the reference of Pace et al., there is no evidence that the polypeptide encoded by SEQ ID NO:1 interacts with Fhit. In the absence of such evidence, there is no indication that knowledge of a Fhit-Nit2 interaction is "widespread". Nor is there evidence that extensive similarities between Fhit and members of the nitrilase family were well known in the art at the time of the invention. It should be noted that applicants' arguments cannot take the place of evidence (see MPEP 716.01(c) and 2145). Contrary to applicants' arguments, the standard for meeting the "substantial" prong of the utility requirement is whether further experimentation is required to identify a "real world" use for the claimed invention. MPEP 2107.01 states, "[u]tilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities". The question of "routine" versus "undue" experimentation is important for assessing whether the specification has taught how to make and use the invention as asserted therein. Further experimentation for determining what the use is leads to a conclusion that the use is not substantial. Even assuming arguendo that the teachings of Pace et al. (*Curr Biol* 10:907-917) were available to one of skill in the art at the time of the invention – which they were not – further experimentation is required to identify

a "real world" context of use for the claimed polynucleotide as evidenced by, e.g., Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9), who teach "the Nit substrate, cell biology and relationship to tumor suppression are not known" (page 7, right column, bottom). See *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in *Brenner v. Manson*, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion".

Applicants argue that, given the likely involvement of the claimed sequence in cancer, one example of utility is tracking expression of the claimed sequences using DNA chips. Applicants argue that since the sequences are specific markers of chromosome 3 and such markers are targets for the discovery of drugs associated with human disease, a skilled artisan would recognize the claimed sequences would be an "ideal, novel candidate" for use in gene expression analysis with DNA chips. Applicants argue that due to the widespread utility of gene chips using public domain gene information, there can be little doubt that the claimed sequences would have utility in DNA chip applications. Applicants argue that compositions that enhance the utility of such DNA chips must themselves be useful. Applicant's argument is not found persuasive.

As previously stated, there is no evidence in the specification that indicates that SEQ ID NO:1 or the polypeptide encoded thereby is involved in cancer. In fact, there is no evidence of record or line of reasoning to indicate that, at the time of filing, the claimed sequences were involved in *any* disease. Regarding applicants' assertion that the sequences are specific markers of chromosome 3, it is noted that there is disclosure in the specification or prior art that the claimed sequence is transcribed from chromosome 3 or is useful as a marker thereof. Regarding the asserted utility of using the claimed sequences in gene expression monitoring using gene chips, it is noted that any sequence can be included as a component of a gene chip – this utility is not specific to the claimed sequences and instead applies to the general class of nucleic acids as evidence by applicants' own statement regarding the widespread use of such gene chips using public domain gene sequences. It is also noted that the claims

are drawn to polynucleotide sequences – not to the physical DNA chip itself or methods of use thereof. Moreover, any information derived from gene expression analysis using the claimed sequences would be meaningless as the specification fails to provide guidance for interpreting any result of expression analysis obtained using the claimed polynucleotide.

Applicants argue that evidence of "real world" substantial utility, is further provided by the alleged fact that there is an entire industry established based on the use of gene sequences in DNA chip format. Applicants argue that the use of gene sequences is a "real world" substantial, widespread and well-established utility. Applicants argue that the utility of genomic data, and specifically human genomic data is well recognized and cite Venter et al. and Jasny et al. as allegedly supporting their argument. Applicant's argument is not found persuasive.

Evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, e.g., a pet rock, wherein the products would not have met the legal standards for utility under 35 USC § 101. In this case, there is no dispute as to the potential usefulness of information obtained from the sequencing of the human genome. However this information is valuable to the extent that it provides a starting point for scientists to further investigate the biological significance of the collected genetic information. In the absence of any information as to the interpretation of a result obtained by gene expression analysis using a DNA chip, the claimed sequences are useful only for further experimentation to investigate their biological significance. As such, the asserted utility of gene expression analysis is not a substantial utility. In the instant case, applicants have failed to demonstrate a patentable utility for the claimed invention.

Applicants argue the specification details the involvement of the claimed sequence in cancer (citing page 1, line 29 of the specification) and state that the examiner's argument that there is no evidence in the specification that indicates that SEQ ID NO:1 or the polypeptide encoded thereby is involved in cancer does not support the lack of utility. Applicants argue that the examiner appears to require an example in the specification demonstrating that the presently claimed sequence has a role in cancer and that there is no statutory requirement for such a specific example.

As previously stated, it should be noted that the specification fails to assert that the polynucleotide of SEQ ID NO:1 or the polypeptide encoded thereby is involved in cancer. Instead, the specification asserts that "[e]nzyme abnormalities have thus been associated with, inter alia, growth, development, protein and cellular senescence, cancer, or other diseases" (page 1, lines 27-29) and there is no disclosed abnormality associated with the polypeptide encoded by SEQ ID NO:1 that is correlated with any of the disclosed disorders, including cancer. Even assuming the specification made an assertion that the claimed polynucleotide is involved in or has a role in cancer, it is noted that this is not an assertion of utility as it is unclear as to how a skilled artisan is to use the polynucleotide based on such an assertion. Even if such a use for SEQ ID NO:1 or the polypeptide encoded thereby were asserted, e.g., for use in treating or detecting cancer, the specification fails to provide the guidance necessary for a skilled artisan to treat or detect cancer using the claimed polynucleotide. Also, it is noted that even after the filing of the instant application, it was known in the art that the relationship of Nit2 (which is 100% identical to the polypeptide encoded by SEQ ID NO:1) to tumor suppression is not known (Pace et al. *Genome Biol* 2:reviews0001.1-0001.9). Contrary to applicants' arguments, the examiner has not required "an example in the specification... ...demonstrating that the presently claimed sequence has a role in cancer." Instead, it is the examiner's position that: 1) the specification fails to assert that SEQ ID NO:1 or the polypeptide encoded thereby is involved in cancer; 2) the specification fails to provide any evidence of a correlation between SEQ ID NO:1 and the polypeptide encoded thereby to cancer; 3) the specification fails to assert a use that is related to cancer for the claimed polynucleotide or encoded polypeptide; and 4) the specification fails to provide guidance for using the claimed polynucleotide or encoded polypeptide for a use that is related to cancer.

Applicants reiterate their argument that the alleged "widespread knowledge" of the interaction between Fhit and nitrilase family members, along with the extensive similarities between Fhit and members of the nitrilase family strongly argues that the skilled artisan would believe that the presently claimed sequence is involved in cancer and the examiner's argument does not support a lack of utility. Applicants' argument is not found persuasive.

As stated above, applicants have provided no evidence that the claimed polynucleotide is involved or related to cancer. Also, applicants have provided no evidence of the alleged "widespread knowledge" of Fhit-nitrilase interaction and the alleged extensive similarities between Fhit and members of the nitrilase family were well known in the art at the time of the invention and MPEP 716.01(c) makes clear that applicants' arguments cannot take the place of evidence. Contrary to applicants' arguments, the standard for meeting the "substantial" prong of the utility requirement is whether further experimentation is required to identify a "real world" use for the claimed invention. MPEP 2107.01 states, "[u]tilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities". Even assuming arguendo that the teachings of Pace et al. (*Curr Biol* 10:907-917) were available to one of skill in the art at the time of the invention – which they were not – further experimentation is required to identify a "real world" context of use for the claimed polynucleotide as evidenced by, e.g., Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9), who teach "the Nit substrate, cell biology and relationship to tumor suppression are not known" (page 7, right column, bottom). See *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. As stated in *Brenner v. Manson*, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion".

Applicants' argue the examiner's assertion that the use of sequences in gene expression monitoring is flawed in two respects: 1) only expressed sequences can be used to track gene expression and that skilled artisans have used and continue to use sequences such as applicants' in gene chip applications without further experimentation and 2) applicants reiterate their argument that the examiner has confused the requirements for a specific utility with a unique utility (citing *Carl Zeiss Stiftung v. Renishaw plc* (CAFC) 20 USPQ2d 1094 . Applicants argue an invention does not need to be the best or only way to accomplish a certain result. Applicants argue the question of whether or not other nucleic acids can be used to assess expression patterns is irrelevant to the instant rejection and that the only question that is relevant is whether every nucleic acid can be use to assess expression patterns, which

applicants assert is no. Applicants argue that the holding in *Carl Zeiss Stiftung* (supra) is mandatory legal authority that directly rebuts the examiner's argument. Applicants' argument is not found persuasive.

It should be noted that there is no evidence of record to support applicants' allegation that skilled artisans have used and continue to use the claimed sequence in a DNA chip. The asserted utility of using the claimed sequence for monitoring gene expression is neither specific nor substantial. *Any* expressed or non-expressed sequence can be used for gene expression monitoring – this utility is not specific. In this case the information provided by gene expression analysis is meaningless (as described in detail above) as the specification fails to provide any guidance as to how one would interpret data obtained from such an analysis. Regarding a unique utility, applicants mischaracterize the examiner's position as applicants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. An invention certainly can have a utility that is shared by other compounds or compositions. On the other hand, not every utility will satisfy 35 USC § 101, even if the utility is shared by a class of inventions. So while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101. Here, applicants assert that the claimed polynucleotides can be used in gene expression analysis. However, as stated above, any results obtained thereby would have no meaning without additional experimentation. Applicants' assert the use of a polynucleotide to measure its own expression is a patentable utility. However, MPEP 2107.01, citing examples of utilities that are not substantial, states, "[a] method of assaying for or identifying a material that itself has no specific and/or substantial utility". As the claimed polynucleotide has no asserted specific and substantial utility or a well-established utility, the use of the claimed polynucleotide for assaying its own expression is not a substantial utility, in accordance with MPEP 2107.01.

Applicants argue that the requirement for a unique utility is not the standard adopted by the USPTO. Applicants argue that the examiner appears to require a specific technical feature for the claimed invention, which is not applicable to the question of utility in a US patent application. Applicants' argument is not found persuasive.

Contrary to applicants' assertion, the examiner has not required a utility that is unique or for applicants to identify a "specific technical feature" of the invention. Instead, the examiner has required only a specific and substantial asserted utility in accordance with MPEP 2107.01. As previously stated, an invention certainly can have a utility that is shared by other compounds or compositions. On the other hand, not every utility will satisfy 35 USC § 101, even if the utility is shared by a class of inventions. So while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101.

Applicants argue that a skilled artisan would understand the meaning of the results of gene expression analysis using the claimed sequence in light of the "well-established" interaction between Fhit and Nit2 and therefore the alleged direct role in that particular cancer tissue. Applicants argue that because there is an entire industry established based on the use of gene sequences in DNA chip format, a skilled artisan would not need guidance for interpreting the result of gene expression analysis as a patent need not disclose that which is well known. Applicants' argument is not found persuasive.

There is no evidence of record of the alleged "widespread knowledge" of Fhit-Nit2 interaction at the time of the invention. Other than Pace et al. (*Curr Biol* 10:907-917), which was published after the filing of the instant application, the examiner can find no teaching of an interaction between Fhit and Nit2. Furthermore, there is no evidence of record to support applicants' allegation that the claimed polynucleotide has a direct role in cancer. In fact, Pace et al. (*Genome Biol* 2:reviews0001.1-0001.9), which was published after the filing of the instant application, teach that the biological significance of Nit2 is not known by stating, "the Nit substrate, cell biology and relationship to tumor suppression are not known" (page 7, right column, bottom). Applicants are reminded that their arguments cannot take the place of evidence (see MPEP 716.01(c) and 2145). Even if the teachings of Pace et al. were known in the art at the time of the invention – which they were not – a skilled artisan would not be able to interpret the results of gene expression monitoring as the specification fails to provide such guidance.

Applicants argue that evidence of commercial success directly rebuts the examiner's allegation that the claimed polynucleotide has no "real world" use and is not useful in currently available form. Applicants argue that the widespread use of gene chips using public domain gene sequences is direct

evidence that the claimed polynucleotide is useful in currently available form. Applicants' argument is not found persuasive.

It should be noted that there is no evidence of record to indicate that the claimed polynucleotide has any commercial value or commercial success. Even if such were the case – which, based on the evidence of record, it is not – as stated above, many products have enjoyed commercial success due to fads or clever advertising, e.g., a pet rock, wherein the products would not have met the legal standards for utility under 35 USC § 101. In the absence of any information as to the interpretation of a result obtained by gene expression analysis using a DNA chip, the claimed sequences are useful only for further experimentation to investigate their biological significance – particularly in view of the teachings of Pace et al. who substantiate the lack of information regarding the biological significance of Nit2 (which is identical to the polypeptide encoded by SEQ ID NO:1). As such, the asserted utility of gene expression analysis is not a substantial utility. In the instant case, applicants have failed to demonstrate a patentable utility for the claimed invention.

Applicants argue that non-expressed nucleic acids cannot be used for gene expression monitoring and request that the examiner provide evidence that a non-expressed sequence can be used for gene expression monitoring. Applicants argue that absent such evidence, the examiner's argument is without merit. Applicants' argument is not found persuasive.

It is noted that the use of a non-expressed nucleic acid, i.e., a nucleic acid that is not transcribed, for gene expression monitoring can certainly be practiced. Although a nucleic acid may not be expressed, this in itself does not preclude the use of a non-expressed nucleic acid for being used in gene expression monitoring.

Applicants argue that only one credible assertion of utility is required and that the claimed polynucleotide has utility for determining the genomic structure of the gene encoding the claimed sequence. Applicants argue the claimed sequence provides "exquisite specificity" in localizing the specific region of human chromosome 3 and that this specificity is useful because it is allegedly shared by virtually no other sequences. Applicants argue SEQ ID NO:1 can be used to map the 9 coding exons on

chromosome 3. Applicants cite Venter et al. as allegedly supporting their argument. Applicant's argument is not found persuasive.

Any expressed human polynucleotide, *e.g.,* a transcript or cDNA, can be used to detect a particular locus of the corresponding gene, therefore *any* human polynucleotide which encodes a protein can be used to determine the specific chromosome which contains that locus. Regarding identification of a *specific* region of human chromosome 3 using the claimed sequences, it is noted that, at the time of filing of the instant application, there was no evidence of record or line of reasoning to suggest that the claimed sequences were useful for identifying any specific region of chromosome 3 or that the region comprising the claimed sequences was shared by virtually any other nucleic acids – this is undisputed by applicants. Based on the specification, this would have required further experimentation and thus, this utility would not be substantial. In regard to the use of the claimed polynucleotides in producing a genetic map of high resolution, it is noted that this use is not specific since many other expressed polynucleotides as indicated above can be used in a similar way. In this case, the asserted utilities are applicable to the broad class of nucleic acids sequences.

Applicants argue that only a minor portion of the genome contains exons. Applicants argue that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce a transcript and that splice junctions can be "hot spots" for events leading to cancer. Applicants argue the claimed polynucleotides provide biologically verified exon splice junctions. Applicants argue the specification asserts that sequences adjacent to intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations that can be used for diagnostic and pharmacogenomic purposes. Applicants argue that the value of biologically validated sequences is apparent to those skilled in the art. Applicants' arguments are not found persuasive.

Such utilities do not meet the specific and substantial requirements of 35 USC § 101. It should be noted that the gene corresponding to the claimed polynucleotide has not been disclosed in the specification. Furthermore, it should be noted that the specification fails to disclose the alleged intron/exon boundaries, the presence of "hot spots" therein, or the presence of mutations within the

claimed polynucleotide or the corresponding gene. Thus, further experimentation is required to determine whether such "hot spots" or mutations occur, and if so, their biological significance, if any.

Applicants reiterate their argument that the examiner has confused the requirements for a specific utility with a unique utility (citing *Carl Zeiss Stiftung v. Renishaw plc* (CAFC) 20 USPQ2d 1094 . Applicants argue that, although other nucleic acids can be used to map this region of chromosome 3, this does not mean this use is not a specific utility. Applicants argue an invention does not need to be the best or only way to accomplish a certain result. Applicants argue the question of whether or not other nucleic acids can be used to assess expression patterns is irrelevant to the instant rejection and that the only question that is relevant is whether every nucleic acid can be use to assess expression patterns, which applicants assert is no. Applicants argue that the holding in *Carl Zeiss Stiftung* (supra) is mandatory legal authority that directly rebuts the examiner's argument. Applicants' argument is not found persuasive.

It should be noted that, at the time of filing of the instant application, there was no evidence of record or line of reasoning to suggest that the claimed sequences were useful for identifying *any* specific region of chromosome 3 or that the region comprising the claimed sequences was shared by virtually no other nucleic acids. Applicants mischaracterize the examiner's position as they have been required to identify a utility that is specific to the invention claimed – not a unique utility. An invention certainly can have a utility that is shared by other compounds or compositions. On the other hand, not every utility will satisfy 35 USC § 101, even if the utility is shared by a class of inventions. So while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101. Applicants' assert the use of a polynucleotide to measure its cognate gene is a patentable utility. However, MPEP 2107.01, citing examples of utilities that are not substantial, states, "[a] method of assaying for or identifying a material that itself has no specific and/or substantial utility". As there is no well-established utility for the gene corresponding to the claimed polynucleotide, the asserted utility is not specific and substantial, in accordance with MPEP 2107.01.

Applicants argue that a statement of utility must be accepted absent reasons to doubt the objective truth of such a statement (citing *In re Langer* and *In re Marzocchi*). Applicants argue that the Federal Circuit in *Juicy Whip Inc. v. Orange Bang, Inc.* has stated that the threshold of utility is not high

and that an invention is useful under § 101 if it is capable of providing some identifiable benefit. Applicants further cite *Brooktree Corp. v. Advanced Micro Devices, Inc.* to indicate that the Federal Circuit has stated that a claimed device must be totally incapable of achieving a useful result to lack utility under 35 USC § 101. Applicants cite *Cross v. Iizuka* in support of their argument that any utility for a claimed invention is sufficient to satisfy the requirements of 35 USC § 101 and indicate that the Federal Circuit has confirmed that anything "under the sun" made by man is patentable in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*

Applicants' arguments appear to address the issue of credibility of an asserted utility. However, the examiner has not questioned the credibility of applicants' asserted use of the claimed polynucleotide. Instead, it is the examiner's position that the specification provides no specific and substantial asserted utility for the claimed invention. It is noted that *Cross v. Iizuka* is considered most relevant to the instant discussion since the inventions in that case are chemical compounds. In *Juicy Whip Inc. v. Orange Bang, Inc.,* the issue of utility was discussed in regard to a juice dispenser, in *Brooktree Corp. v. Advanced Micro Devices, Inc.,* the issue of utility was discussed in regard to digital analog conversion circuitry, and in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.,* the issue of utility was discussed in regard to a business method. As stated above, the claimed invention has no specific and substantial utility as the asserted utilities are applicable to the broad class of polynucleotides and/or require further experimentation to identify a "real world" use. It should be noted that in *Cross v Iizuka*, the specification disclosed the structure of the claimed imidazole derivative compounds and the specification provided experimental evidence of inhibition of thromboxane synthetase inhibition by these imidazole derivatives in human and bovine microsomes and a method for practicing such. In the instant case, the specification fails to provide guidance for practicing <u>any</u> patentable utility of the claimed sequences. Thus, in contrast to *Cross v Iizuka,* the claimed invention fails to benefit the public in currently available form. Even assuming that *Juicy Whip Inc. v. Orange Bang, Inc., Brooktree Corp. v. Advanced Micro Devices, Inc., Cross v. Iizuka,* and *State Street Bank & Trust Co. v. Signature Financial Group, Inc.* are relevant to the instant rejection, it is noted that the instant rejection does not contradict the cited case law.

Applicants argue the examiner discounts the cited case law and that the cited case law is mandatory legal authority whose precedents must be followed by the examiner. Applicants argue that 35 USC 101 makes no distinction between that which is claimed. Applicants' argument is not found persuasive.

Contrary to applicants' assertion, the examiner has not discounted the cited case law. The examiner has fully considered applicants' arguments in accordance with MPEP 707.07(f). Instead, the examiner has identified case law that is most relevant to the instant claims, i.e., the utility of claims drawn to chemical compounds. Moreover, it is noted that the instant rejection does not contradict the findings in the cited case law.

Applicants argue that the widespread use of nucleic acid sequences in numerous applications for assessing gene expression patterns and mapping protein-coding regions of chromosomes, is direct evidence that the claimed invention benefits the public in currently available form. Applicants' argument is not found persuasive.

As previously stated, the asserted use of the claimed polynucleotide for gene expression monitoring and chromosome mapping is neither specific (all expressed polynucleotides can be used for such applications) nor substantial (further experimentation is required to establish a "real-world" use).

Applicants argue that even if further research is required, this does not preclude a finding that the invention has patentable utility (citing *In re Brana*). Applicants argue the need for some experimentation does not render the invention unpatentable and that a considerable amount of experimentation may be permissible if routine. Applicants argue that absent evidence, one of ordinary skill in the art would understand the claimed invention has patentable utility. Applicant's argument is not found persuasive.

In *Brana,* the claimed invention was shown to have patentable utility based on evidence provided in the specification demonstrating *in vitro* anticancer activity of the claimed compound. The court found the claimed invention to have patentable utility based on the asserted "antitumor activity". The claimed invention had patentable utility in its currently available form without further experimentation. The court's statement regarding "the expectation of further research and development" was directed to Phase II experiments to confirm antitumor activity *in a human,* however, it should be noted that no further

experimentation was required to confirm the use of the claimed invention for *in vitro* antitumor activity, i.e., the claimed invention was useful in a currently available form without need for further experimentation. In this case, further experimentation is required to establish a "real world" use for the claimed polynucleotide. Thus, the asserted utilities are not substantial, in accordance with MPEP 2107.01, which states, "[u]tilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities".

Applicants indicate that the requirements set forth in the Office action for compliance with 35 USC § 101 do not comply with the requirements set forth by the PTO itself for complying with 35 USC § 101. Applicants state that, while they are aware of the new utility guidelines set forth by the USPTO, the current rules and regulations are the patent laws set forth in 35 USC and the rules set forth in 37 CFR but not the MPEP or guidelines set forth by the USPTO. Applicants argue it is the job of the judiciary and not the USPTO to interpret these laws and rules. Applicants argue that they are unaware of recent changes in either 35 USC § 101 or in the interpretation of 35 USC § 101 by the Supreme Court or the Federal Circuit which support the new utility guidelines set forth by the USPTO. Applicants cite patents that allegedly do not contain examples of the "real world" utilities allegedly required by the Examiner. Applicants argue that holding them to a different standard of utility would be arbitrary and capricious. Applicants argue that the guidelines followed by the USPTO should not be confused with the force of law. Applicants argue there are numerous examples of USPTO guidelines that have been found not to comport with the patent laws and rules and cite *In re Brana* as an alleged example of the Federal Circuit overturning USPTO-enacted guidelines.

Applicants are respectfully reminded that the examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the examiner has no authority to disregard such guidelines or to apply his own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the USPTO in accordance with all applicable case law and thus are believed to be consistent therewith. While the examiner acknowledges the cited US patents, each patent application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO

and a discussion on the utility of any polynucleotide claimed in such patents would require a detailed review of the record of each individual case, which would be improper. Finally, applicants are further reminded that the examiner has no authority to comment in regard to the legality of the current utility guidelines or the MPEP as set forth by the USPTO.

[3] Status of claims:

- Claims 1-3 and 5-7 are pending in the application.
- Claims 1-3 and 5-7 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652

04-02-04